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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/945,203	08/31/2001	Mark J. Espy	07039-247001	4479

26191 7590 06/18/2003

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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/945,203	ESPY ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1/2002* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). It is noted that claim 6 has been omitted.

Accordingly, claims numbered 7-37 have been renumbered to claims 6-36

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-26 in the response filed on April 13, 2003 is acknowledged.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code(See for ex. Pg. 17, line 1). See MPEP § 608.01.

Priority

Acknowledgement of the provisional application filed 08/31/2000 drawn to this same subject matter has been made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1, 4-16, 19, 20, and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sauerbrei et al.(Journal of Clinical Virology, 1999) in view of Wittwer et al.(US Patent 6,174,670).

Sauerbrei et al. teach virological diagnosis of zoster in vesicle fluid and swabs from the dermatomes of the chest, head, neck, waist, and pelvis in addition to serum sample(32). The reference teaches a study of biological samples of 100 patients with zoster being analyzed by detecting DNA using PCR. The findings were compared with those obtained by traditional virological and serological methods. Primers and probes specific for VZV gene 28 and 29 were used for amplification and detection of the VZV DNA by PCR(Table 1). The results of this study show that PCR detects VZV in zoster with a high rate of sensitivity and specificity. PCR results were available within 1 day and showed no cross-reaction to HSV. The reference therefore teaches that PCR with primers of genes 28 and 29 is the method of choice for rapid diagnosis of zoster. Primers for genes 28 and 29 are both necessary to detect the maximum number of cases, as taught by the reference's Table 2. The reference further teaches the use of positive and negative controls and furthermore "there were no cross-reactions to VZV with any of the oligonucleotides used (specificity 100%)"(34) in their provision for preventing amplification of a contaminant nucleic acid.

Sauerbrei et al. do not teach a FRET based PCR detection method, nor do they teach the subtleties of the PCR reaction asserted in the remaining claims.

However, Wittwer et al. (US Patent 6,174,670) teach a method of PCR amplification for the detection of viral polynucleotides, specifically for the PCR-amplified products of hepatitis B virus(See for example, FIG 37-39 and 41A&B), but the reference teaches a general method applicable to detection of any virus. The reference teaches a method for detecting the presence or absence of any virus and exemplifies amplification of Hepatitis B in a biological sample from an individual, said method comprising:

performing at least one cycling step, wherein a cycling step comprises an amplifying step and a hybridizing step, wherein said amplifying step comprises amplifying a portion of a viral nucleic acid molecule from said biological sample using a pair of viral specific primers, thereby producing an amplification product specific to the hepatitis virus, wherein said hybridizing step comprises hybridizing a pair of probes to said amplification product, wherein the members of said pair of probes hybridize within no more than five nucleotides of each other, wherein a first probe of said pair of probes is labeled with a donor fluorescent moiety(fluorescein, Col. 4) and said second probe of said pair of probes is labeled with a corresponding acceptor fluorescent moiety(Cy5TM or Cy5.5TM Col. 4);(See Abstract, Brief Summary of Invention) and Fig. 18 for example) and

detecting the presence or absence of fluorescence resonance energy transfer(FRET) between said donor fluorescent moiety of said first probe and said acceptor fluorescent moiety of said second probe upon hybridization of said pair of probes to said amplification product, following excitation of the biological sample at a wavelength absorbed by said donor fluorescent

moiety and visualizing and/or measuring the wavelength emitted by said acceptor fluorescent moiety, after each cycling step, all in real time(Col.5 and Col.19 for example).

wherein the presence of FRET is indicative of the presence of the hepatitis virus in said biological sample, and wherein the absence of FRET is indicative of the absence of hepatitis virus in said biological sample and further wherein the melting temperature of the amplification product confirms said presence or said absence of said virus being tested(Col 7, for example). Wittwer et al. further teaches the above method comprising preventing amplification of a contaminant nucleic acid(DETX 163 and 143 and 148 for example), and furthermore in claims 73-78 the use of a selected control template and corresponding primers and probes with which it may be detected. Lastly, Wittwer et al teach the above method wherein the presence of said FRET within 50, 40, and 30 steps is indicative of the presence of a hepatitis infection, or generally a viral infection in said individual(See for example Fig.20-27 and corresponding text).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to have practiced the FRET-based viral detection method of Wittwer using PCR with primers of genes 28 and 29 as the method of choice for rapid diagnosis of Zoster since primers for genes 28 and 29 are taught by Sauerbrei et al. to be necessary to detect the maximum number of Varicella-Zoster cases. It is further true that as current methods of PCR carry out temperature cycling slowly and empirically and additional time consuming steps are required, this method of Wittwer provides a great advance in the art for monitoring hybridization during PCR and analyzing the reaction while it is taking place, that is, during or immediately after temperature cycling without manipulation of the sample(Col.3). The reference concludes that by monitoring hybridization during PCR, the underlying principles that allow PCR to work

can be followed and used to analyze and optimize a PCR reaction during amplification. As a whole then, the combined teachings of Sauerbrei et al. and Wittwer provide a more accurate method for the early detection of a VZV infection.

2. Claims 1, 4-20, and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sauerbrei et al.(Journal of Clinical Virology, 1999) in view of Wittwer et al.(US Patent 6,174,670) and in further view of Longo et al.(Gene, 1990).

The combined references of Sauerbrei and Wittwer teach as stated above, the FRET-based PCR method with specific primers and probes for genes 28 and gene 29 of VZV. The references do not teach however the steps of claims 16 and 17 involving preventing amplification of a contaminant nucleic acid.

However, Longo et al. teach the step of preventing amplification of a contaminant nucleic acid comprising performing said amplifying step in the presence of uracil and through the further treatment of the biological sample with uracil-DNA glycosylase prior to a first amplifying step(Summary). Longo et al teach that carry-over contamination of new PCRs by the abundant amplification products can be a significant problem, due to the abundance of PCR products, and to the ideal structure of the contaminant material for re-amplification.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to have added the steps of Longo et al to the method of Sauerbrei et al. in view of Witter et al. in order to have prohibited these chances of contamination and thereby the chance of obtaining false positives.

3. Claims 1-16, 19, 20-22 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davison et al.(J. gen. Virol. 1986) in view of Rose et al.(US Patent 5,925,733) and in further view of Wittwer et al.(US Patent 6,174,670).

Davison et al. teach the complete DNA sequence of Varicella-Zoster virus including genes 28 and 29 and SEQ ID NOS: 1-8. Through their analysis of the sequence, the reference teaches a genome containing 70 genes distributed about equally between the two DNA strands. The discerned organization of VZV genes and that deduced for herpes simplex virus type 1 (HSV-1) from published transcript mapping data indicate that these two members of the *Alphaherpesvirinae* are very similar in gene layout(Summary). Comparisons of the predicted amino acid sequences of VZV proteins with those available for HSV-1 proteins generally suggest evolution from an ancestral genome, and allow the functions of several VZV genes to be deduced. The reference also teaches the usefulness of comparisons between VZV and HSV-1, as these viruses possess several conserved genes arranged colinearly in the genomes. The hypothesis resulting from this finding is that the two genomes have similar gene arrangements and was confirmed by the reference's comparison of the VZV gene layout deduced from the DNA sequence with that of HSV-1 proposed from currently available transcript mapping and sequence data. Consequently, the functions of several VZV genes can be identified on the basis of our knowledge of the molecular genetics of HSV-1, which far exceeds that of any other herpesvirus(Pg. 1760). The reference further specifically teaches properties of the proteins coded by predicted VZV genes 28 and 29 as DNA polymerase and Major DNA-binding proteins respectively(Table 1), the reference further teaches the position of each gene's start and stop codons and their molecular weights. The reference's sequence provides a firm foundation on

which to build a detailed understanding of VZV infection at the molecular level. This knowledge may be applied in the development of effective treatments for the diseases caused by this virus. The sequence has also given the first complete view of the gene layout in the *Alphaherpesvirinae,* and has allowed our knowledge of the proposed functions of VZV genes to increase from almost nothing to equal that of HSV-1.

Davison et al. do not teach their varicella-zoster genomic sequence in the form of specific gene 28 primers and probes used in a FRET based PCR detection method, nor do they teach the subtleties of the PCR reaction embodied by claims 4-16 and 19.

However, Rose et al. teach the specific gene 28 primers and probes used in a PCR based detection assay using fluorescently-labeled probes(Col. 40), and further that altering the number of amplification cycles to obtain the desired fragment as being a routine matter for a practioner of ordinary skill in the art(Col. 32) The reference thus teaches the detection of VZV through the use of oligonucleotides, shown in their table 4, that are generally useful for hybridizing with DNA polymerase encoding polynucleotide segments(UL30, gene 28) isolated from biological samples such as blood, spinal fluid, and other liquid samples of biologic origin(Col. 23). The reference teaches that this may be conducted to detect the presence of the polynucleotide, or to prime an amplification reaction so that the polynucleotide may be characterized further. Rose et al. teach that suitable targets include polynucleotides encoding a region of a DNA polymerase from a wide spectrum of herpes viruses, including human varicella-zoster(Table 1 and Col. 31). The reference further teaches making these primers specific to UL30, a DNA Polymerase(aka gene 28 and SEQ ID NOS:1-4) and using them in an amplification reaction to hybridize to the target DNA and thereby act as a primer for the polymerization reaction(Col.32). The reference

further teaches the use of 2 additional oligonucleotides as probes in a detection assay(Col. 34). The reference thus teaches using SEQ ID NOS 1-4 in the context of detecting Varicella-Zoster virus in a PCR based method. Lastly, the kits of this method teach control samples, the reagent that renders the procedure specific: a reagent polynucleotide, used for detecting target DNA as well as means of detection(Col. 53).

Rose et al does not exemplify the exact PCR method steps used in the present invention's FRET-based assay.

However, Wittwer et al. (US Patent 6,174,670) teach a method of PCR amplification for the detection of viral polynucleotides, specifically for the PCR-amplified products of hepatitis B virus(See for example, FIG 37-39 and 41A&B), but the reference teaches a general method applicable to detection of any virus. The reference teaches a method for detecting the presence or absence of any virus and exemplifies amplification of Hepatitis B in a biological sample from an individual, said method comprising:

performing at least one cycling step, wherein a cycling step comprises an amplifying step and a hybridizing step, wherein said amplifying step comprises amplifying a portion of a viral nucleic acid molecule from said biological sample using a pair of viral specific primers, thereby producing an amplification product specific to the hepatitis virus, wherein said hybridizing step comprises hybridizing a pair of probes to said amplification product, wherein the members of said pair of probes hybridize within no more than five nucleotides of each other, wherein a first probe of said pair of probes is labeled with a donor fluorescent moiety(fluorescein, Col. 4) and said second probe of said pair of probes is labeled with a corresponding acceptor fluorescent

moiety(Cy5TM or Cy5.5TM Col. 4);(See Abstract, Brief Summary of Invention) and Fig. 18 for example) and

detecting the presence or absence of fluorescence resonance energy transfer(FRET) between said donor fluorescent moiety of said first probe and said acceptor fluorescent moiety of said second probe upon hybridization of said pair of probes to said amplification product, following excitation of the biological sample at a wavelength absorbed by said donor fluorescent moiety and visualizing and/or measuring the wavelength emitted by said acceptor fluorescent moiety, after each cycling step, all in real time(Col.5 and Col.19 for example).

wherein the presence of FRET is indicative of the presence of the hepatitis virus in said biological sample, and wherein the absence of FRET is indicative of the absence of hepatitis virus in said biological sample and further wherein the melting temperature of the amplification product confirms said presence or said absence of said virus being tested(Col 7, for example). Wittwer et al. further teaches the above method comprising preventing amplification of a contaminant nucleic acid(DETX 163 and 143 and 148 for example), and furthermore in claims 73-78 the use of a selected control template and corresponding primers and probes with which it may be detected. Lastly, Wittwer et al teach the above method wherein the presence of said FRET within 50, 40, and 30 steps is indicative of the presence of a hepatitis infection, or generally a viral infection in said individual(See for example Fig.20-27 and corresponding text).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to detect the sequences of Davison et al. through the PCR method of Rose et al in view of Wittwer et al. The prospect of detecting an infectious varicella-zoster virus polynucleotide sequence in light of the teachings of the conserved nature of the DNA polymerase

encoding sequences of all herpes virus, would provide the motivation necessary to practice the combined teachings of Davison and Rose and detect gene 28(DNA polymerase encoding) in a PCR-based method with specific primers and probes taught for gene 28 by the sequences of both Davison and Rose. Furthermore, Wittwer's teachings of a FRET based PCR method used to detect viral components, would have been further obvious to incorporate into the teachings of Davison and Rose, as current methods of PCR carry out temperature cycling slowly and empirically and additional time consuming steps are required. Thus, this method of Wittwer provides a great advance in the art for monitoring hybridization during PCR and analyzing the reaction while it is taking place, that is, during or immediately after temperature cycling without manipulation of the sample(Col.3). The reference concludes that by monitoring hybridization during PCR, the underlying principles that allow PCR to work can be followed and used to analyze and optimize a PCR reaction during amplification. As a whole then, the combined teachings of Davison, Rose and Wittwer provide a more accurate method for the early detection of a VZV infection at the molecular level(Davison, Pg. 1813).

4. Claims 1-19, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davison et al(J. gen. Virol, 1986) in view of Rose et al.(US Patent 5,925,733) and Wittwer et al.(US Patent 6,174,670) and in further view of Longo et al.

In view of the combined teachings of a FRET-based PCR method of detecting VZV of Davison, Rose, and Wittwer stated above, these references do not teach however the steps of claims 16 and 17 involving preventing amplification of a contaminant nucleic acid.

However, Longo et al. teach the step of preventing amplification of a contaminant nucleic acid comprising performing said amplifying step in the presence of uracil and through the further treatment of the biological sample with uracil-DNA glycosylase prior to a first amplifying step(Summary). Longo et al teach that carry-over contamination of new PCRs by the abundant amplification products can be a significant problem, due to the abundance of PCR products, and to the ideal structure of the contaminant material for re-amplification.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to add the steps of Longo et al in order to have prohibited these chances of contamination and thereby the chance of obtaining false positives.

5. Claims 20-22 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over as being unpatentable over Davison et al(J. gen. Virol, 1986) in view of Rose et al.(US Patent 5,925,733) and Wittwer et al.(US Patent 6,174,670) and further in view of Beards et al. (Journal Medical Virol. 1998).

In view of the combined teachings of a FRET-based PCR method of detecting VZV of Davison, Rose, and Wittwer stated above, these references do not teach gene 29 specific primers and probes with which to practice the method.

However, Beards et al. teach 4 sets of specific primers for gene 29 and VZV detection(156). It should be further noted that the reference's teaching of a nested primer, PCR system including 4 different sets of primer pairs, provides a motivation for using the nested primers alternatively as probes for the expected benefit of providing a more specific PCR product.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have supplemented the teachings of Davison, Rose, and Wittwer with the primers/probes specific for gene 29 of the VZV for the expected benefit of obtaining a more accurate diagnostic method for the presence of the virus.

SEQUENCE ALIGNMENTS

Please see attached alignments of SEQ ID NOS: 1-8 with the sequence of the Davison reference, and SEQ ID NOS: 1-4 with the sequences of the Rose et al. reference. No sequence is free of the prior art.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)308-1119. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris
6/11/2003

CARLA J. MYERS
PRIMARY EXAMINER